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Robotic-assisted laparoscopic hysterectomy for women with endometrial cancer

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ABSTRACT

INTRODUCTION: Robotic-assisted laparoscopic hysterectomy (RALH) has become a widely used approach for women with endometrial cancer and has replaced laparotomy. It has been questioned if the increased costs are justified by superior surgical outcomes. The aim of the present study was to examine the frequency, types and severity of post-operative complications after total abdominal hysterectomy (TAH) and RALH using the Clavien-Dindo classification of surgical outcomes.

METHODS: A non-randomised, controlled before and after study of 360 women was conducted; 202 underwent RALH and 158 TAH (historical controls).

RESULTS: RALH had significant advantages compared with TAH: fewer and less severe post-operative complications and a shorter length of hospital stay. The absolute risk reduction for post-operative complications was 13% (95% confidence interval: 4.29-20.87%). Women treated with TAH had significantly more severe complications (grade ≥ 3) than those treated with RALH; 12% versus 3% (p = 0.001). Infections (urinary and port site) were the most frequent post-operative complications overall. The duration of RALH in the operation theatre was longer, while the duration of stay in the post-anaesthesia care unit was shorter for patients undergoing RALH.

CONCLUSIONS: RALH appears advantageous for women treated for endometrial cancer in terms of post-operative complications. We recommend the use of the Clavien-Dindo classification of surgical outcomes for quality assessment.

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TRIAL REGISTRATION: Danish Health Authority (3-2013-111/1/KAHO).

Endometrial cancer is the most common cancer in the female genital tract in the developed world with an incidence of 11-14 per 100,000 in Europe [1]. In high-income countries, a sedentary lifestyle and the obesity epidemic play a major role in the rising incidence [2]. Endometrial cancer is most frequently detected in elderly post-menopausal women with multiple comorbidities.

Treatment for endometrial cancer is hysterectomy (HYS) and bilateral salpingo-oophorectomy (BSO). Lymph node involvement is an important prognostic factor [3]. In Denmark, cases with more than 50% myoinvasion or high-risk histology are offered pelvic lymphadenectomy (PLA). Danish guidelines recommend that atypical complex hyperplasia (ACH) be treated as endometrial cancer.

Previously, the standard procedure for HYS was laparotomy. Nevertheless, HYS by laparoscopy has not been widely used in gynaecologic oncology. The limitations of laparoscopy include counterintuitive motion, non-wristed instrumentation which contributes to a difficult and long learning curve [4]. Since 2005 when the US Food and Drug Administration approved robotic-assisted laparoscopy for use in gynaecology, there has been a rapid dissemination of this technique. The robotic technique brings the advantages of minimally invasive surgery: less post-operative morbidity and earlier recovery. Robotic-assisted surgery also has the specific advantages of 3-D-vision, higher magnification, better ergonomic conditions for surgeons and a shorter learning curve than for conventional laparoscopy. The disadvantages are lack of tactile feedback and high costs. In Denmark during the 2013-2014-period, more than 50% of women with endometrial cancer or ACH were treated by robotic-assisted laparoscopic hysterectomy (RALH), approximately 21% by laparotomy and 22% by laparoscopy [5]. At our centre, however, laparoscopy has not been used for this indication.

We lack evidence from randomised clinical trials (RCTs) comparing RALH with conventional open HYS in regard to post-operative complications. However, given the widespread adoption of RALH in clinical settings and patients' preferences, it is probably no longer feasible to conduct randomised clinical trials. Nevertheless, in light of the increasing economic burden on our healthcare systems, the question persists whether the greater expenses associated with robotic surgery are justified by superior surgical outcomes [6]. Some studies have presented their initial experiences with RALH [7] and confirm that robotic surgery has a short learning curve. For this reason, we wanted to compare the outcomes of RALH, excluding learning cases. This *controlled before and after study* aimed to examine the outcomes of total abdominal hysterectomy (TAH) by laparotomy versus robotic-assisted HYS – both as implemented standard procedures. The primary outcome was the frequency, types

ORIGINAL ARTICLE

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TABLE 1

Baseline characteristics (N = 360).

	Type of hysterectomy		
	total abdominal (N_1 = 158)	robotic-assisted laparoscopic (N_2 = 202)	p-value
Diagnosis, n (%)			
Endometrial cancer	150 (95)	165 (82)	< 0.001[a]
Atypical complex hyperplasia	8 (5)	37 (18)	
Age, mean (± SD), yrs	68.5 (10.8)	68 (11.3)	0.66[b]
Body mass index			
Mean (± SD), kg/m^2	27.7 (7.4)	28.5 (7.1)	0.36[b]
Obese ≥ 30 kg/m^2, n (%)	51 (32)	75 (37)	0.34[a]
Daily smoker, n (%)	20 (13)	23 (11)	0.74[b]
> 7 units alcohol/week, n (%)	17 (11)	49 (24)	0.002[a]
ASA-score, n (%)			0.09[a]
I & II	138 (87)	167 (83)	
III	17 (11)	35 (17)	
Missing	3 (2)	–	
Cardiovascular disease[c], n (%)	78 (49)	99 (49)	1.0[a]
Respiratory disease[d], n (%)	7 (4)	15 (7)	0.27[a]
Diabetes Type II, n (%)	20 (13)	21 (10)	0.51[a]

ASA = American Society of Anesthesiologists; SD = standard deviation.
a) Fisher's exact test.
b) Independent samples t-test.
c) Hypertension, atrial fibrillation, arteriosclerotic heart disease, heart failure New York Heart Association Classification of Heart Failure: 1) cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc. 2) mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
d) Chronic obstructive pulmonary disease, asthma, emphysema.

ABBREVIATIONS

ACH = atypical complex hyperplasia
BSO = bilateral salpingo-oophorectomy
EBL = estimated blood loss
HYS = hysterectomy
LOS = length of stay
OM = omentectomy
OR = odds ratios
PACU = post-anaesthetic care unit
PLA = pelvic lymphadenectomy
RCT = randomised controlled trial
RALH = robotic-assisted laparoscopic hysterectomy
TAH = total abdominal hysterectomy

and severity of post-operative complications in women treated by HYS for endometrial cancer or ACH.

METHODS

Consecutive patients undergoing RALH were compared with consecutive patients undergoing TAH (historical controls). The primary outcome was the frequency of patients developing one or more post-operative complications requiring treatment. The secondary outcomes were the type and severity of post-operative complication according to the Clavien-Dindo classification of surgical outcomes [8], length of hospital stay (LOS), duration of surgery (skin-to-skin time), duration of anaesthesia, and duration of stay in the post-anaesthetic care unit (PACU). The inclusion criteria were: women diagnosed with endometrial cancer or ACH treated with HYS by TAH (1 March 2006-1 March 2009) or by RALH (1 January 2013-1 September 2014). The follow-up time was four months. We defined post-operative complications as infections requiring antibiotic treatment within 30 days, circulatory complications and abdominal complications requiring treatment within 30 days. Furthermore, we monitored the occurrence of hernia, vaginal cuff dehiscence and lymfocele up to four months post-operatively as these complications are surgically related but may take longer time to develop. We graded the severity of post-operative complications according to the Clavien-Dindo classification of surgical outcomes [8]. We defined severe complications as complications of grade 3 or higher [9].

Previous studies report complication rates in the 6-12% range for women treated by RALH and 20-30% for women treated by TAH [7, 10]. With a minimally relevant difference of 10% points in the frequency of patients developing post-operative complications requiring treatment, α = 5% and β = 20%, power calculations indicated that 141 women were required in each group. We used descriptive statistics with means and standard deviations as appropriate for continuous data and frequencies and percentages for categorical data. To determine differences between groups, Fisher's exact test was used for categorical variables and independent samples t-tests for continuous variables. We determined odds ratios (OR) by using binary logistic regression presented with and without adjustments for potential confounders. When there was a low number of events in the adjusted analysis, we only included potential confounders with a univariate p-value < 0.2 in addition to variables that were unbalanced at baseline. All calculated p-values were two-sided, and < 0.05 was considered statistically significant. To correct for mass significance, we used Bonferroni correction for test on post-operative outcomes. We analysed data using SPSS version 19.9 (Inc., Chicago, Il, USA).

Robotic-assisted laparoscopy at Herlev and Gentofte Hospital.

We have reported the study according to the STROBE statement for observational studies [11]. The National Council for Data Protection gave permission to file data (2207-58-015/HEH.750.16-27). The Danish Health Authority (3-2013-111/1/KAHO) and the head of the department of gynaecology Herlev and Gentofte Hospital, approved the acquisition of data from patient charts and hospital records.

Trial registration: Danish Health Authority (3-2013-111/1/KAHO).

RESULTS

We included 360 women, 158 had TAH and 202 had RALH. Age, BMI, smoking, ASA score and comorbidity did not differ between the groups (**Table 1**). More women had ACH and more women exceeded seven units of alcohol per week in the RALH group. Women treated by RALH had a significantly lower estimated blood loss (EBL), longer skin-to-skin time, longer duration of anaesthesia, shorter duration of stay in the PACU and shorter LOS than women treated by TAH (**Table 2**). In all three-time measurements, a significant difference was found between TAH and RALH (**Figure 1**).

Women in the TAH group had a significantly higher frequency of one or more post-operative complications than the RALH group, 26% versus 13% (p = 0.003). The absolute risk reduction was 13% (95% confidence interval (CI): 4.29-20.87%) (Table 2). With respect to the severity of post-operative complications, women treated by TAH developed significantly more severe post-operative complications (grade ≥ 3) than those treated by RALH; 12% versus 3% (p = 0.001) (**Table 3**). The adjusted OR for one or more post-operative complications in the RALH group was 0.39 (95% CI: 0.21-0.72) (p = 0.003). The adjusted OR for developing a Clavien-Dindo grade ≥ 3 post-operative complication in the RALH group was 0.24 (95% CI: 0.08-0.69) (p = 0.008).

3% in the TAH group developed intraoperative complications (lesion of the bladder n = 1, lesion of the intestine n = 2, and lesion of larger vessels n = 2) compared with 1% in the RALH group (lesion of the bladder n = 2). Infections (urinary and port site) were the most frequent post-operative complication overall. In each group, one woman had a stroke post-operatively and two deaths occurred. A 70-year-old woman developed vaginal haematoma, pulmonary embolus and urosepsis and died three months after TAH. An 88-year-old woman developed urosepsis and ileus and died three weeks after RALH with conversion to open surgery.

In the TAH group, 85 (54%) had HYS and BSO as opposed to 153 (76%) in the RALH group. In the TAH group, 73 (46%) had HYS, BSO, PLA and/or omentectomy (OM) as opposed to 49 (24%) in the RALH group (p < 0.001). The mean number of lymph nodes resected was 20 in both groups; in the RALH group, conversion to TAH occurred in four (2%) women.

Subgroup analysis excluding women who had more extensive surgery (PLA and/or OM) (n = 238) did not change the overall results, but showed 26% with post-operative complications in the TAH group versus 13% in the RALH group (p = 0.02). Using the Clavien-Dindo classification of surgical outcomes, the corresponding figures were 12% in the TAH group with post-operative complications grade ≥ 3 versus 3% in the RALH group (p = 0.007). However, when we analysed only women with HYS + BSO and PLA and/or OM (n = 122), the frequency of post-operative complications between the groups did not differ significantly; 26% in the TAH group versus 14% in the RALH group (p = 0.18). Likewise, the frequency of post-operative complications of grade ≥ 3 according to the Clavien-Dindo classification did not differ significantly; 12% in the TAH group versus 4% in the RALH group (p = 0.2).

TABLE 2

Findings and complications (N = 360).

	Type of hysterectomy		
	total abdominal (N_1 = 158)	robotic-assisted laparoscopic (N_2 = 202)	p-value
Intraoperative			
Intraoperative bleeding, mean (± SD), ml	299 (± 275)	41 (± 58)	< 0.001[b, c]
Skin-to-skin time[a], mean (± SD), min.	102 (± 34)	120 (± 46)	< 0.001[b, c]
Anaesthesia time[a], mean (± SD), min.	180 (± 62)	221 (± 70)	< 0.001[b, c]
PACU time[a], mean (± SD), min.	455 (± 221)	186 (± 119)	< 0.001[b, c]
Post-operative			
Length of stay, mean (± SD), days	6 (± 3.5)	3 (± 1.8)	< 0.001[b, c]
Readmission within 30 days, n (%)	16 (10)	15 (7)	0.45[d]
Reoperation within 30 days, n (%)	11 (7)	6 (3)	0.09[d]
Complications, n (%)			
Infections within 30 dayse	27 (17)	22 (11)	–
Abdominal complications within 30 days[f]	9 (6)	6 (3)	–
Circulatory complications within 30 days[g]	9 (6)	2 (1)	–
Long-term surgically related within 4 mo.s[h]	6 (4)	2 (1)	–
Frequency of post-operative complication			
≥ 1 complications[i, j], n (%)	41 (26)	27 (13)	0.003[c, d]

PACU = post-anaesthetic care unit; SD = standard deviation.
a) For detailed time measurements for subgroups see Figure 1.
b) Independent samples t-test.
c) Also significant after Bonferroni correction for mass significance (α = 0.005/8 = 0.000625).
d) Fisher's exact test.
e) Port site/wound infection, intraabdominal infection, infection with unknown focus, vaginal cuff infection, urinary tract infection, pneumonia, sepsis, gastroenteritis.
f) Wound rupture, intraabdominal bleeding, ulcer/gastritis, vesico-vaginal fistula, ileus.
g) Pulmonary oedema, myocardial infarction, pulmonary embolism, deep vein thrombosis, stroke.
h) Vaginal cuff dehiscence, hernia, lymfocele.
i) 6 women had 2, and 2 women had 3 post-operative complications in the TAH group; 3 women had 2, and 1 had 3 post-operative complications in the RALH group.
j) Absolute risk reduction: 26–13 = 13 (95% confidence interval: 4.29-20.87) %-points.

FIGURE 1

Mean time measures in minutes*.

BSO = bilateral salpingo-oophorectomy; HYS = hysterectomy; PACU = post-anaesthetic care unit; PLA/OM = pelvic lymphadenectomy and/or omentectomy; RALH = robotic-assisted laparoscopic hysterectomy; TAH = total abdominal hysterectomy.
*) Significant differences between the RALH and the TAH groups for HYS + BSO and for HYS + BSO and PLA/OM measured for all three-time measures by independent samples t-tests.

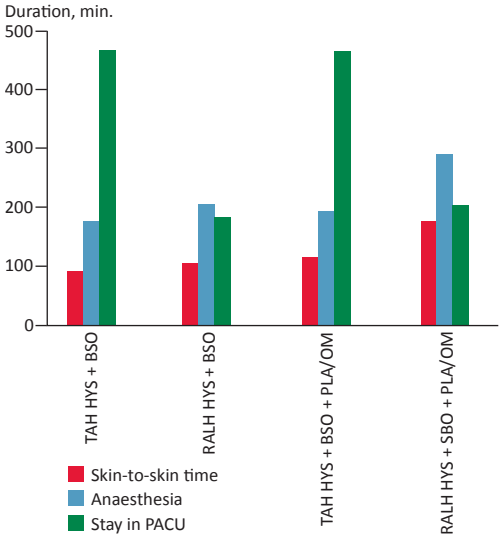

TABLE 3

Severity of complications according to the Clavien-Dindo classification of surgical outcomes[a]. The values are n (%).

	Type of hysterectomy		
Grade	total abdominal (N = 158)	robotic-assisted laparoscopic (N = 202)	p-value
1	5 (3)	14 (7)	
2	32 (20)	28 (14)	
≥ 3			
3[a]	3 (2)	0	
3[b]	14 (9)	5 (3)	
4[a]	2 (1)	0	
4[b]	0	0	
5	0	1 (< 1)	
Sub-total[b]	19 (12)	6 (3)	0.001[c]

a) Severe complications are defined as complications of grade ≥ 3 (for the definition of grades, see [8]).
b) Absolute risk reduction: 12-3 = 9 (95% confidence interval: 3.7-15.3) %-points.
c) Fisher's exact test.

DISCUSSION

In this study, women in the RALH group developed fewer and less severe post-operative complications than those undergoing TAH. Complications in the RALH group were primarily infections. Diabetes, obesity and high age can increase the risk of infections and are all predominant risk factors in women with endometrial cancer [3]. The observed 3% frequency of grade 3 or higher post-operative complications according to the Clavien-Dindo classification of surgical outcomes in the RALH group may be considered quite low for this type of surgery. The frequency observed here is similar to that observed in women undergoing robotic HYS for benign indications (2.4-3.1%) [9, 12]. These studies also used the Clavien-Dindo classification of surgical outcomes to assess complications, which enables direct comparison across populations and centres. The RALH group had a lower EBL and a shorter LOS. A reduced EBL is desirable as it decreases the post-operative recovery time for patients. Compared with laparotomy, a shorter LOS is a well-known positive outcome of minimally invasive surgery, for patients and health costs alike [13].

At baseline, more women in the RALH group exceeded seven units of alcohol per week. Adjustment for this baseline difference in alcohol consumption did not change the significantly decreased risk of developing one or more complications in the RALH group.

The data in this study did not reflect a RALH learning period for surgeons. However, skin-to-skin time and duration of anaesthesia in the RALH group were significantly longer than in the TAH group, which concurs with findings reported by other studies [14]. The mean difference in skin-to-skin time was 18 minutes in favour of TAH in our study. Our mean skin-to-skin time in the robotic group (120 minutes) is close to the findings reported from studies of women treated with HYS for benign indication (105 minutes) [9]. In the present study, the mean skin-to-skin time was 173 minutes for HYS + SBO and PLA and/or OM by RALH. Previous studies of HYS, BSO and lymphadenectomy for endometrial cancer reported longer mean skin-to-skin times (189-191 minutes) [10, 15], whereas others reported shorter skin-to skin times (127 minutes) [16, 17]. As robotic surgery becomes more and more routine, skin-to-skin time is likely to be minimised. For example, recent studies of open versus robotic surgery for endometrial cancer showed a significant difference in skin-to-skin time in favour of the robotic group [16, 17].

Some of the changes in LOS and duration of stay in the PACU seen in this study across the two time periods may be due to an increased turnover in the PACU and in hospitals in general. At baseline, we found a difference in the number of women who had PLA and/or OM performed in the two groups. A reason for this could be that recent years have seen further centralisation of the treatment of gynaecologic cancer in Denmark resulting in more women with ACH being treated at specialised centres. Subgroup analysis excluding women undergoing more extensive surgery did not change the significant reduction in the frequency or severity of complications in favour of RALH.

Apart from the patient advantages and better ergonomics for surgeons, it has been suggested that robotic surgery is superior especially when operating morbidly

obese patients. It is considered better to sit in a console and be able to adjust the height of the stereoscopic viewer, the arm rest and the position of the pedals to accommodate the operating surgeon's body length than to stand at the operating table. However, a recent online survey study of 432 robotic surgeons working in general surgery, gynaecology and in urology showed that 56% of surgeons experienced physical symptoms or discomfort [18]. The most frequent symptoms were neck and finger stiffness and eye fatigue [18], suggesting that the new surgical work position might produce new ergonomic problems while diminishing others.

A strength of this study is the exclusion of learning cases. We used the validated Clavien-Dindo classification of surgical outcomes, which enables comparison across populations owing to its widespread use in surgical studies. This was an observational "controlled before and after study" and a limitation of this design is the risk of confounding leading to biased estimates of treatment effects [19]. Effects of different interventions are preferably evaluated in RCTs. However, we considered that an observational design was the only feasible option within the field of gynaecologic robotic surgery given the current widespread adoption of robotic surgery as standard treatment.

Further limitations of this study include the use of historical controls and retrospective collection of data. We sought to address the latter by using the Clavien-Dindo classification of surgical outcomes, which is particularly relevant in retrospective analyses as it identifies complications specifically from the documentation of therapy to treat a complication rather than from documentation of the complications [20]. RALH had advantages compared with TAH in women with endometrial cancer and atypical complex hyperplasia, including significantly fewer and less severe complications, less bleeding and a shorter LOS than TAH. Robotic surgery takes longer in the operating theatre, but shortens the duration of stay in the PACU.

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